

Role of Early Enteral Nutrition in Mechanically Ventilated COVID-19 Patients

OBJECTIVES: Current guidance recommends initiation of early enteral nutrition (early EN) within 24–36 hours of ICU admission in critically ill COVID-19 patients. Despite this recommendation, there is quite limited evidence describing the effect of early EN on outcomes in COVID-19 patients. The association between early EN (within 3 d post intubation) and clinical outcomes in adult COVID-19 patients requiring mechanical ventilation (within 2 d post ICU admission) was evaluated.

DESIGN: We performed a nationwide observational cohort study using a nationwide administrative-financial database (Premier) in United States.

SETTING: Information pertaining to all COVID-19 patients admitted to ICU from 75 hospitals between April and December 2020 was analyzed.

PATIENTS: A total of 861 COVID-19 patients were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Clinical outcomes were assessed via regression models to control for patient and hospital characteristics. We identified 513 COVID-19 ICU patients (59.2%) requiring mechanical ventilation who received early EN and had similar baseline characteristics to late EN group. Compared with late EN group, the early EN group had shorter ICU (hazard ratio [HR], 1.39; 95% CI, 1.15–1.68) and hospital length of stays (LOS) (HR, 1.53; 95% CI, 1.23–1.91), fewer mechanical ventilation days (HR, 1.25; 95% CI, 1.01–1.54), and lower cost (–\$22,443; 95% CI, –\$32,342 to –\$12,534). All comparisons were statistically significant ($p < 0.05$).

CONCLUSIONS: In patients with COVID-19 requiring mechanical ventilation, early EN is associated with earlier liberation from mechanical ventilation, shorter ICU and hospital LOS, and decreased cost. Our results are among the first to support guideline recommendations for initiation of early EN in COVID-19 ICU patients. Further, our data show nearly 40% of critically ill COVID-19 patients fail to have early EN initiated, even at 3 d post initiation of mechanical ventilation. These results emphasize the need for targeted strategies promoting initiation of early EN, as this may lead to improved clinical and economic outcomes in severe COVID-19 patients.

KEY WORDS: COVID-19; critical illness; intensive care unit; nutrition; patient outcomes; severe acute respiratory syndrome coronavirus 2

Enteral nutrition (EN) is recommended by societal guidelines to be initiated within 24–36 hours of admission or 12 hours after intubation in critically ill COVID-19 patients (1). Further, recent literature indicates nutritional status in COVID-19 patients is an independent risk factor for in-hospital mortality and is associated with poor clinical outcomes (2). The complex clinical course of severe COVID-19, including gastrointestinal involvement and severe acute respiratory syndrome, often makes it challenging to achieve practice recommendations for early EN (3). Despite published recommendations highlighting importance of early EN, there is a notable lack of evidence

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describing its association with outcome and hypothesized benefit in COVID-19 patients undergoing mechanical ventilation (MV). Given discordance between existing evidence and guideline recommendations, we examined the association between early EN (within 3 d of intubation) and outcomes among mechanically ventilated COVID-19 patients in one of the nation's largest inpatient databases, the Premier Healthcare Database.

METHODS

Data Source

This was a retrospective cohort study approved by Duke University Health System's Institutional Review Board (IRB) (Duke IRB Number: Pro00105510) that used a nationwide administrative, financial database (Premier Healthcare Database; Premier, Charlotte, NC). This database includes patient and hospital demographics, *International Classification of Diseases*, 10th revision (ICD-10) procedure and diagnosis codes, as well as billing information to form a detailed date-specific billing record for each patient during a hospital admission. The Premier database represents approximately 20% of all discharges for annual inpatients in 75 hospitals.

Study Population

All adult (≥ 18 yr) COVID-19 patients who underwent MV within 2 days after hospital admission and had received EN for at least 2 days between April and December 2020 were included in the analysis. We identified patients with a primary or secondary diagnosis of COVID-19 (ICD-10 code: U07.1). Laboratory confirmation of COVID-19 was unavailable in the database, but the accuracy of ICD based diagnosis for COVID-19 has been validated in the previous study (4). We specifically excluded patients who did not receive MV within 2 days of admission or who did not receive EN for at least 2 days at some point in their hospitalization, and those who died within 7 days of hospital admission.

Exposure

We compared patients who began EN within 3 days of intubation (early EN) to patients who began EN greater than or equal to 4 days after intubation (late EN) determined by the presence of day-stamped hospital charge codes for EN.

Outcome

The primary outcome was in-hospital mortality during the index hospitalization. We also assessed hospital and ICU length of stay (LOS), MV days, and total cost as the secondary outcomes.

Covariates

Key covariates controlled for and included in the models were age group, male, race, payor category, congestive heart failure, chronic obstructive pulmonary disease, obesity, chronic kidney disease, acute respiratory distress syndrome (ARDS), early vasopressor, early hemodialysis, bed size (≥ 500), teaching status, and location (rural or urban). The selected comorbidities were identified using the binary Elixhauser's comorbidity indicators (5). ARDS was identified ICD-10 diagnosis codes (J80). Since severity of illness scores were not available in the dataset, we restricted the cohort into patients with MV and included early vasopressor and hemodialysis as a proxy to severity of illness in the models. Inverse-probability-of-treatment weighting (IPTW) was used to control for confounding variables on observable characteristics.

Statistical Analysis

Data were presented as mean \pm SD or percentages, as appropriate. Either the chi-square or Fisher exact test was used for nominal variables, and unpaired *t* tests were used to compare continuous variables. In order to account for immortal time bias in this study, we used a landmark analysis by measuring hospital death after 7 days of admission (6). The multivariable logistic regression model was fit for hospital mortality, and the multivariable linear regression model was fit for cost. Cox proportional hazard models with death treated as a censored observation were used to determine the association of early EN versus late EN with hospital discharge (LOS) and ICU discharge (ICU LOS). We chose the cause-specific Cox model over the Fine-Gray because we were interested in the direct association between the exposure and LOS (7). We adjusted for all covariates mentioned above. A type I error rate of 0.05 was set as the threshold for statistical significance. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 861 patients who met inclusion criteria after 265,298 patients were excluded. The exclusions were due to patients 17 years old or younger ($n = 2268$), no MV within 2 days of admission ($n = 246,719$), no receipt of EN for at least 2 days during ICU stay ($n = 16,239$), and death with 7 days of admission

($n = 72$). Overall, 513 patients (59.2%) received early EN. The mean age was 62.2 ± 14.4 years, 60.1% were male, and 47.1% were Caucasian. The early EN group was more likely to be in large-sized hospitals (45.5% vs 39.9%; $p = 0.007$) (Table 1). Only six patients of 861 received total parenteral nutrition in the study group (1/512 in early EN group and 5/343 in late group). The mean time to EN initiation in early EN group was

TABLE 1.
Baseline Characteristics of Mechanically Ventilated COVID-19 ICU Patients

Baseline Characteristics	Total Cohort <i>N</i> = 861	Early EN <i>N</i> = 513	Late EN <i>N</i> = 348	<i>p</i>
Age, \pm SD (yr)	62.2 \pm 14.4	62.6 \pm 14.5	61.7 \pm 14.4	0.36
Age groups, <i>n</i> (%)				0.74
20–29	21 (2.4)	11 (2.1)	10 (2.9)	
30–39	45 (5.2)	25 (4.9)	20 (5.7)	
40–49	83 (9.6)	53 (10.3)	30 (8.6)	
50–59	176 (20.4)	103 (20.1)	73 (21)	
60–69	249 (28.9)	141 (27.5)	108 (31)	
70–79	198 (23)	124 (24.2)	74 (21.3)	
\geq 80	89 (10.3)	56 (10.9)	33 (9.5)	
Male, <i>n</i> (%)	526 (61.1)	317 (61.8)	209 (60.1)	0.61
Race, <i>n</i> (%)				0.23
Asian	33 (3.8)	25 (4.9)	8 (2.3)	
African American	249 (28.9)	143 (27.9)	106 (30.5)	
Caucasian	399 (46.3)	235 (45.8)	164 (47.1)	
Other	180 (20.9)	110 (21.4)	70 (20.1)	
Payer category, <i>n</i> (%)				0.21
Managed care organization	149 (17.3)	91 (17.7)	58 (16.7)	
Medicaid	138 (16)	72 (14)	66 (19)	
Medicare	419 (48.7)	251 (48.9)	168 (48.3)	
Other	155 (18)	99 (19.3)	56 (16.1)	
Comorbidity, <i>n</i> (%)				
Congestive heart failure	198 (23)	123 (24)	75 (21.6)	0.41
Chronic obstructive pulmonary disease	205 (23.8)	123 (24)	82 (23.6)	0.89
Obesity	328 (38.0)	183 (35.7)	145 (41.7)	0.08
Chronic kidney disease	204 (23.7)	124 (24.2)	80 (23)	0.69
Early vasopressor, <i>n</i> (%)	388 (45.1)	231 (45)	157 (45.1)	0.98
Early hemodialysis, <i>n</i> (%)	56 (6.5)	33 (6.4)	23 (6.6)	0.92
Teaching hospital, <i>n</i> (%)	519 (60.3)	318 (62)	201 (57.8)	0.21
Rural hospital, <i>n</i> (%)	128 (14.9)	83 (16.2)	45 (12.9)	0.19
Bed size (\geq 500), <i>n</i> (%)	392 (45.5)	253 (49.3)	139 (39.9)	0.007

EN = enteral nutrition.

Student *t* test was used for continuous variables; χ^2 and Fisher exact test were used for categorical variables.

2.4 ± 0.8 days and 9.9 ± 8.4 days (with a minimum of 4 d) in late EN group (**Table 2**).

In regression models, the early EN group had shorter ICU LOS (hazard ratio [HR], 1.39; 95% CI, 1.15–1.68) (**Table 3**) and hospital LOS (HR, 1.53; 95% CI, 1.23–1.91), fewer MV days (HR, 1.25; 95% CI, 1.01–1.54), and lower cost (–\$22,443; 95% CI, –\$32,342 to –\$12,534) compared with the late EN group. Hospital mortality was not significantly different between groups (odds ratio, 0.91; 95% CI, 0.67–1.23).

DISCUSSION

This current study of real-world clinical practice shows early EN was significantly associated with earlier liberation from MV, shorter ICU and hospital LOS, and reduced hospital costs in COVID-19 ICU patients. Our results support current guideline recommendations for initiation of early EN. Further, our data show nearly 40% of COVID-19 ICU patients fail to have early EN initiated, even by 3 days post initiation of MV.

Despite clinical guidelines recommending early EN in the ICU (1, 8), the clinical benefits of early EN continue to remain the subject of long-standing debate. However, randomized controlled trials have demonstrated early EN (initiated within 24–36 hr post ICU admission) in non-COVID-19 ICU patients leads to reductions in hospital LOS, infection rates, and mortality (9). These findings in non-COVID-19 ICU patients have been extended, without published evidence to this point, to serve as the basis for the current guidance from the American Society for Parenteral and EN (ASPEN) and Society of Critical Care Medicine (SCCM) recommending early EN in COVID-19 ICU patients.

A recent study compared early (within 24 hr) with late (post 24 hr) EN in 100 matched COVID-19 patients on MV. The authors found no significant difference in LOS, hospital mortality, or MV-free days.

Conversely, our study of real-world clinical practice identified an association with significant benefit of initiating EN within 3 days of MV. The difference in findings observed between our study and that of Farina et al (10) could be associated with the larger cohort of patients included in our analysis and examining initiation of EN within 3 days, which may be a more clinically achievable target versus 24 hours. Long-standing research has shown early EN within 12 hours, or even 48 hours, after start of MV can be quite challenging to achieve (11). A review article reported that when intensivists were surveyed regarding their reasoning behind delayed EN in COVID-19 patients, the most common reason was fear of aspiration in patients with limited respiratory reserve coupled with concern for an often-unpredictable clinical course (3). Additional challenges to early EN include the common use of prone positioning as clinicians are often hesitant to feed patients in prone position for fear of aspiration. In contradiction to this concern, recent data summarized in SCCM/ASPEN COVID-19 ICU nutrition guidelines show EN during prone positioning is safe, not correlated with increased pulmonary complications, and these guidelines recommend EN in prone patients (1).

Use of vasopressor support has also traditionally led to concerns about the risk of potential complications with early EN. Data show that patients requiring vasopressor support may actually benefit from early EN as shown in an observational trial of greater than 50,000 patients where early EN within 48 hours of ICU admission was associated with lower mortality rates while on low- or medium-dose norepinephrine doses (up to 0.3 µg/kg/min) (12). Current guidelines recommend early EN in non-COVID-19 and COVID-19 ICU patients requiring ongoing vasopressor support post resuscitation (1, 8).

Finally, it is now well understood that COVID-19 can infect the gastrointestinal tract and lead to

TABLE 2.

Time to Initiation of Enteral Nutrition in Early Enteral Nutrition and Late Enteral Nutrition Groups in Mechanically Ventilated COVID-19 ICU Patients

Group	n	Mean	SD	Minimum	25th Percentile	50th Percentile (Median)	75th Percentile	Maximum
Early EN	513	2.4	0.8	1	2	2	3	3
Late EN	348	9.9	8.4	4	5	7	12	62

EN = enteral nutrition.

TABLE 3.
Univariable and Multivariable Results Comparing Early Enteral Nutrition With Late Enteral Nutrition Among Mechanically Ventilated COVID-19 Patients

Outcomes	Univariable Analyses			Multivariable Analyses	
	Early EN N = 513	Late EN N = 348	p	Yes (Reference = Late EN)	p
				Odds ratio (95% CI)	
Hospital mortality, n (%)	341 (39.6)	202 (39.4)	0.87	0.91 (0.67–1.23)	0.55
				Hazard ratio (95% CI)	
LOS, d, median (IQR)	18.0 (12.0–30.0)	25.0 (16.5–38.0)	< 0.001	1.54 (1.21–1.97)	< 0.001
ICU LOS, d, median (IQR)	14.0 (8.0–22.0)	17.0 (11.0–27.0)	< 0.001	1.41 (1.14–1.74)	0.002
Mechanical ventilation, d, median (IQR)	12.0 (8.0–20.0)	15.0 (9.0–25.0)	0.004	1.28 (1.01–1.62)	0.042
				Estimate (95% CI)	
Total cost, mean ± SD	\$87,144 ± 73,048	\$118,610 ± 96,095	< 0.001	–19,626 (–29,531 to –9,721)	< 0.001

EN = enteral nutrition, IQR = interquartile range, LOS = length of stay.

Covariates included in the models were age group, male, race, payor category, congestive heart failure, chronic obstructive pulmonary disease, obesity, chronic kidney disease, acute respiratory distress syndrome, early vasopressor, early hemodialysis, bed size (≥ 500), teaching status, and location (rural or urban). Hazard ratio > 1 means the hazard of discharge alive is shorter in early EN compared with late EN.

significant gastrointestinal complications, making delivery of early EN even more challenging to achieve. Our data support that it is critical to address all potential barriers to EN delivery. Further, our study describes for the first time to our knowledge that in real-world clinical practice, nearly 40% of COVID-19 ICU patients are not receiving early EN by even ICU day 3. This corroborates that significant barriers and challenges remain in motivating initiation of early EN in COVID-19. It further highlights that an even more significant number of COVID-19 ICU patients are failing to receive guideline recommended early EN initiation within 24–36 hours, a shorter time frame than considered in this study (1).

Early EN initiation may ultimately prove to have a more significant impact on clinical outcomes in critically ill COVID-19 patients as recent literature reports the hypermetabolism associated with severe COVID-19 maybe more significant and prolonged versus non-COVID-19 ICU patients (13). Our group recently performed a longitudinal study using indirect calorimetry in mechanically ventilated COVID-19 ICU patients and found over the course of ICU stay COVID-19 patients have a significantly higher measured resting energy expenditure (REE) versus equation-predicted REE (13). Furthermore, we found

COVID-19 patients can demonstrate a persistent hypermetabolic state even out to 7 weeks post ICU admission. This hypermetabolic state often persists considerably beyond the 7–10-day acute hypermetabolic phase described previously in other non-COVID-19 ICU patients (13).

Cost differences between early EN and late EN were evaluated using a large-scale analysis. As a result of improved clinical outcomes, total cost of acute hospital care for early EN was reduced by \$14,462/patient. Similarly, we saw a cost reduction ranging between \$23,047 and \$31,466 in the early EN group compared with the late EN group. These findings highlight the importance and effectiveness of early EN in reducing the overall economic burden of COVID-19 to U.S. health-care systems. Early implementation of EN protocols may be a cost-effective way to reduce hospital related healthcare costs while improving patient outcomes.

This study has several limitations. First, this study did not account for total caloric intake or advancement of EN over time. Second, although we were able to evaluate the contribution of comorbidities in these patients, we were unable to analyze their baseline nutritional status before having COVID-19, which could have led to unmeasured confounding. Third, we used a multihospital, real-world database, and accordingly,

there was no standard protocol for starting early EN, and decision to start EN was made by each clinician using their own criteria. Accordingly, the decision to start early EN may be itself a marker of illness severity that could effect the decision to initiate EN. This limitation could potentially lead to confounding by indication. Fourth, as this is a retrospective analysis, the results demonstrate an association but do not establish causality. Fifth, to account for immortal time bias and because patients who died early may not have had an indication for early EN, we conservatively only included patients survived greater than 7 days post hospital admission.

CONCLUSIONS

Our data suggest that early EN in mechanically ventilated COVID-19 patients may reduce time on MV, shorten ICU and hospital LOS, and decrease hospital costs. Our results are among the first to support guideline recommendations for early EN in COVID-19 ICU patients. Further, our data show nearly 40% of critically ill COVID-19 patients fail to have early EN initiated, even at 3 days post initiation of MV. These results emphasize the need for targeted strategies promoting early EN initiation, as this may lead to improved clinical and economic outcomes in severe COVID-19 patients. Future prospective studies are needed to further assess these findings and verify our results in COVID-19 ICU patients.

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